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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/719,621	11/21/2003	Luis H. Toledo	TOL01 P-100A	3490
Luis Toledo 3598 Whistling Lane Portage, MI 49024			EXAMINER RAO, DEEPAK R	
			ART UNIT	PAPER NUMBER
			1624	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	12/22/2006	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary

Application No.

10/719,621

Applicant(s)

TOLEDO ET AL.

Examiner

Deepak Rao

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 21 August 2006.
2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-10, 13-16 and 18 is/are pending in the application.
4a) Of the above claim(s) _____ is/are withdrawn from consideration.
5) ☒ Claim(s) 1-10 is/are allowed.
6) ☒ Claim(s) 13-16 and 18 is/are rejected.
7) ☐ Claim(s) _____ is/are objected to.
8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

Claims 1-10, 13-16 and 18 are pending in this application.

Withdrawn Rejections/Objections:

Applicant is notified that any outstanding rejection/objection that is not expressly maintained in this office action has been withdrawn or rendered moot in view of applicant's amendments and/or remarks.

The following rejections are maintained:

Claims 13-16 and 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating ischemic stroke, does not reasonably provide enablement for a method of treating **ischemic injury** generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The reasons provided in the previous office action are provided below for convenience:

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed. The determination that "undue experimentation" would have been needed to make and use the claimed invention is not a single, simple factual determination. Rather, it is a conclusion reached by weighing all the above noted factual considerations.

The instant claim 13 is drawn to 'a method of treating a human who has an ischemic disease selected from coronary heart disease, peripheral vascular disease, etc. '. As can be seen from the definitions of the terms "ischemic disease", "coronary heart disease", "peripheral vascular disease", "transplant injuries", they include without limitation many types of diseases and therefore, the claims are seen to

encompass methods of treating a wide variety of diseases. The instant claim appears to be a 'reach through' claim. Reach through claims, in general have a format drawn to mechanistic, receptor binding or enzymatic functionality and thereby reach through any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

There are no testing assays provided in the specification related to the activity of the compounds and applicant did not state on record or provide any guidance regarding types of test assays to find the clinical efficacy of the compounds in the treatment of various disorders of the claims. As can be seen from specification pages 14-15, the dosage regimen is accurately determined 'by measuring the blood level or concentration of the nitroso compounds in the patient's blood and/or the patient's response to the particular condition being treated'.

The instant claims are drawn to "a method treating ischemic disease selected from coronary heart disease, stroke, hemorrhagic shock, peripheral vascular disease, and transplant related injuries". First, the instant claims cover 'diseases' that are known to exist and those that may be discovered in the future, for which there is no enablement provided. The use disclosed in the specification is therapeutic agents for the treatment of ischemic diseases, however, the specification does not provide any test assays or data regarding how the compounds correlate to the treatment of the various disorders of the instant claims. Some of the diseases and disorders encompassed by the instant claims have been proven to be extremely difficult to treat. Further, there is no reasonable basis for assuming that the myriad of compounds embraced by the claims will all share the same physiological properties since they are so structurally dissimilar as to be chemically non-equivalent and there is no basis in the prior art for assuming the same. Note *In re Surrey*, 151 USPQ 724 regarding sufficiency of disclosure for a Markush group.

See MPEP § 2164.03 for enablement requirements in cases directed to structure-specific arts such as the pharmaceutical art. Receptor activity is generally unpredictable and highly structure specific area. It is inconceivable as to how the claimed compounds can treat all types of diseases of the instant claims generally. Further, there is no disclosure regarding how the patient in need of the treatment requiring treatment is identified and further, how all types of the diseases are treated. The state of the art reference, Zhang (Medline Abstract) indicates therapeutic benefits of NO donors during recovery from ischemic stroke.

There is no evidence of record, which would enable the skilled artisan in the identification of the people who have the potential of becoming afflicted with the disease(s) or disorder(s) claimed herein and therefore, require the treatment. Next, applicant's attention is drawn to the Revised Utility and Written Description Guidelines, at 66 FR 1092-1099, 2001 wherein it is emphasized that 'a claimed invention must have a specific and substantial utility'. The disclosure in the instant case is not sufficient to enable the instantly claimed 'treating' effect of a 'disease' solely based on the therapeutic activity stated for the compounds.

The terms 'ischemic diseases', 'coronary heart diseases' and 'peripheral

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vascular diseases' embrace a vast array of problems, many of which are contradictory to others. Thus, the terms cover hypertension and hypotension. Further, the terms include various types of arrhythmias; angina pectoris', the thrombotic symptoms of diabetes, atherosclerosis and hyperlipoproteinaemias, ischemic heart disease including congestive heart failure and myocardial infarction, stroke, and peripheral vascular disorders, such as deep-vein thrombosis and thrombophlebitis percutaneous transluminal coronary angiography (PTCAI; elevated blood levels of triglycerides, of total cholesterol or of LDL cholesterol, arteriosclerosis, peripheral vascular disease, cerebral vascular disease and pulmonary hypertension, migraine, cardiomyopathy, etc. Not one compound -- let alone a genus of thousands of compounds, could possibly be effective against such disorders generally.

The state of the art is not indicative of any nitroso therapeutic agents for treating ischemic diseases in general. The examiner notes, there is not seen sufficient guidance provided to the skilled artisan to practice the therapeutic methods, in the form of administration profiles, combination ratios of the active agents or references to same in the prior art. The diagnosis of each of the disease is generally suggested by medical history and reports of endoscopy, cytology, X-ray, biopsy, etc. depending on the symptoms, signs and complications, which is essential to establish the dosage regimen for appropriate treatment. The disclosure does not provide any guidance towards the dosage regimen required to facilitate the treatment of the claimed disorders, nor indicate competent technical references in the appropriate methods.

Applicants have not provided any competent evidence or disclosed tests to determine the efficacy of the compounds, that are highly predictive for the pharmaceutical use of the instant compounds. Pharmacological activity in general is a very unpredictable area. Note that in cases involving physiological activity such as the instant case, "the scope of enablement obviously varies inversely with the degree of unpredictability of the factors involved". See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The state of the art is not indicative of any therapeutic agents that are generally useful in the treatment of the claimed disorders and therefore, asserts the need of undue experimentation for the instantly claimed therapeutic benefits.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

Thus, factors such as "sufficient working examples", "the level of skill in the art" and "predictability", etc. have been demonstrated to be sufficiently lacking in the use of the invention. In view of the breadth of the claim, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the invention commensurate in scope with the claims.

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Applicant amended claim 13 to recite “A method of treating **ischemic injury** in a human in need thereof” and relies on the amendment to overcome the rejection of the previous office action. The recitation “ischemic injury” however, includes all types of injury or damage caused by the ischemic event. As provided in the specification as well as known from the state of the art, the term ‘ischemia represents restriction or interruption of blood supply in blood vessels, with resultant damage or dysfunction of tissue’. Tissues especially sensitive to the inadequate blood supply are the heart, the kidney and the brain. Therefore, the instantly recited term “ischemic injury” is applicable to diseases of all the tissues associated with various organs, specifically the heart, the kidney and the brain. Thus the term represents a broader range of diseases than previously claimed and applicant has not provided any data or state of the art references to support the instant method claims.

Applicant did not provide any explanation as to how treatment of all types of “ischemic injury” is enabled. Further, one skilled in the art recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to various disease states, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases due to ischemic injury. Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule for treatment of any particular disease. A detailed understanding of the molecular mode of action of the ischemic event alongside the elucidation of the molecular pathology of individual disease is required to identify the disease symptoms and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular

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biomarkers and pharmacokinetic and pharmacodynamic parameters for each individual disease therapeutic intervention.

The following rejections are necessitated by the amendment:

Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 18 depends from a canceled claim (claim 17).

Allowable Subject Matter

Claims 1-10 are allowed. The closest reference of record, U.S. Patent No. 5,380,724 does not teach or fairly suggest the instantly claimed compounds. (see the reasons provided in the previous office action).

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period

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will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Deepak Rao whose telephone number is (571) 272-0672. The examiner can normally be reached on Monday-Friday from 8:00am to 5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson, can be reached at (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).


Deepak Rao
Primary Examiner
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December 19, 2006